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Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Gonadotropin-releasing Hormone Agonists, Orchiectomy, and Risk of Cardiovascular Disease: Semi-ecologic, Nationwide, Population-based Study

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Abstract

Background: In observational studies, men with prostate cancer treated with gonadotropin-releasing hormone (GnRH) agonists had a higher risk of cardiovascular disease (CVD) compared to men who had undergone orchiectomy. However, selection bias may have influenced the difference in risk.

Objective: To investigate the association of type of androgen deprivation therapy (ADT) with risk of CVD while minimising selection bias.

Design, setting, and participants: Semi-ecologic study of 6556 men who received GnRH agonists and 3330 men who underwent orchiectomy as primary treatment during 1992–1999 in the Prostate Cancer Database Sweden 3.0.

Outcome measurements and statistical analysis: We measured the proportion of men who received GnRH agonists as primary treatment in 580 experimental units defined by healthcare provider, diagnostic time period, and age at diagnosis. Incident or fatal CVD events in units with high and units with low use of GnRH agonists were compared. Net and crude probabilities were also analysed.

Results and limitations: The risk of CVD was similar between units with the highest and units with the lowest proportion of GnRH agonist use (relative risk 1.01, 95% confidence interval [CI] 0.93–1.11). Accordingly, there was no difference in the net probability of CVD after GnRH agonist compared to orchiectomy (hazard ratio 1.02, 95% CI 0.96–1.09). The 10-yr crude probability of CVD was 0.56 (95% CI 0.55–0.57) for men on GnRH agonists and 0.52 (95% CI 0.50–0.54) for men treated with orchiectomy. The main limitation was the nonrandom allocation to treatment, with younger men with lower comorbidity and less advanced cancer more likely to receive GnRH agonists.

Conclusion: Our data do not support previous observations that GnRH agonists increase the risk of CVD in comparison to orchiectomy.

Patient summary: We found a similar risk of cardiovascular disease between medical and surgical treatment as androgen deprivation therapy for prostate cancer.

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1. Introduction

Androgen deprivation therapy (ADT) for men with prostate cancer [1,2] is associated with adverse effects such as bone loss with increased risk of fractures [3–5], metabolic aberrations with a higher risk of cardiovascular disease (CVD) [6–14], and a higher risk of diabetes mellitus type 2 [14–16].

It was recently reported that gonadotropin-releasing hormone (GnRH) agonists are associated with a higher risk of CVD compared to orchiectomy [17,18]. However, the difference in risk of CVD between GnRH agonists and orchiectomy may have been confounded by indication for treatment, since men who undergo orchiectomy are on average older and have more advanced prostate cancer than men treated with GnRH agonists, resulting in a shorter life expectancy and less time at risk for CVD [12,17–19].

The aim of this study was to assess the association between type of ADT and risk of CVD, while minimising selection bias. We took advantage of a natural experiment that took place in Sweden during the 1990s, when type of ADT was often more influenced by the preference of the healthcare provider than by a man's prostate cancer characteristics and comorbidity. We performed a semi-ecologic study in which exposure to GnRH agonists was assessed on a population level in experimental units defined by healthcare provider, diagnostic time period, and age at diagnosis, with outcomes assessed on an individual level [20,21]. We also analysed crude and net probability, with exposure and outcome assessed on an individual level [22].

2. Patients and methods

Prostate Cancer Data Base Sweden (PCBaSe) 3.0 contains information on cancer characteristics and primary treatment from the National Prostate Cancer Register (NPCR) of Sweden [23,24]. Information on comorbidity from the Patient Registry and data on educational level, income, and marital status were obtained from the LISA database, and cause and date of death were obtained from the Cause of Death Registry [23,25–31].

The current study included men diagnosed with prostate cancer during 1992–1999 who received GnRH agonists or bilateral orchiectomy as primary treatment (Supplementary Fig. 1).

No data on the date of treatment are available in the NPCR. Therefore, we assessed the time from diagnosis to start of treatment using data from a later calendar period (2006–2012) when these dates were available from other sources. Information in the Prescribed Drug Registry (which started in 2005) for date of first filled prescription for GnRH agonist and data in the Patient Registry (which reached high capture of orchiectomy procedures in the mid-2000s) showed that 90% of men had received their primary treatment within 3 mo after the date of diagnosis. Therefore, follow-up in the current study was started 3 mo after the date of prostate cancer diagnosis, and the men were followed until the event of interest, death, emigration, or end of the study period (December 31, 2013), whichever event came first.

The CVD endpoint was identified as the first occurrence of a CVD diagnosis (ICD-10 codes I00–I99), including hypertension (I10–I15), ischaemic heart disease (I21–I25), stroke (I60–I64, G45), deep venous thrombosis or pulmonary embolism (I80–I93, I26), and arterial embolism (I74, K55), in the Patient Registry or Cause of Death Registry.

The associations between GnRH agonists or orchiectomy and fractures (SX2) and diabetes (E10–E14) were also assessed.

The research ethics board at Umeå University Hospital approved the study.

2.1. Statistical methods

Differences in characteristics between the treatment groups were tested using the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables.

Three analytical approaches were used to compare risk of CVD between men treated with GnRH agonists and men treated with orchiectomy. First, a semi-ecologic study design was applied to assess exposure to treatment on a group level in an attempt to minimise selection bias [20,21]. Exposure was measured as the proportion of men who received GnRH agonists in experimental units defined by healthcare provider, 2-yr diagnostic time period, and age at diagnosis (<70, 70–74, 75–79, 80+ yr). For each of the 580 experimental units, the number of events and person-years at risk were calculated. A Poisson model with the logarithm of person-years at risk as the offset was used to assess the association between the proportion of men who received GnRH agonists, included as a restricted cubic spline, and the risk of a CVD event, with prostate-specific antigen (PSA), T stage, metastases, previous CVD, hypertension, and previous diabetes within 5 yr from diagnosis as covariates. Results are presented as relative risk (RR) with 95% confidence interval (CI).

Using individual data on exposure and outcome, the crude and net probability of CVD were estimated. The crude probability of death from prostate cancer and death from causes unrelated to CVD were calculated in a competing-risks analysis [32]. The net probability of CVD was estimated using the Kaplan-Meier method, and the hazard ratio (HR) and 95% CI were estimated with multivariable Cox proportional hazards models using age as the time scale and censoring observations at the time of the occurrence of a competing event (ie, death from other causes) [33]. The multivariable model included type of treatment (GnRH agonist vs orchiectomy), year of diagnosis (continuous), PSA (categorical), stage (categorical), metastases (categorical), and previous CVD (yes vs no), hypertension (yes vs no), and diabetes (yes vs no) within 5 yr from diagnosis.

All tests were two-sided and the significance level was set to $p < 0.05$. Statistical analysis was performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The study population consisted of 6556 men who received GnRH agonists and 3330 men who underwent orchiectomy as primary treatment. The median follow-up for men alive at the end of follow-up was 16 yr and there was a total of 46 012 person-years of follow-up. There was a sevenfold difference in use of GnRH agonists between experimental units with the lowest and the highest use (14% vs 96%). The use of GnRH agonists increased during the study period (Fig. 1). Men treated with GnRH agonists were younger and had a higher proportion of nonmetastatic disease, lower serum PSA levels, fewer previous CVD events, and higher educational level in comparison to men who underwent orchiectomy (Supplementary Table 1). These differences were smaller when comparing units with high and low use of GnRH agonists, but in the same direction as in the direct comparison between men treated with GnRH agonists and orchiectomy (Table 1).

3.1. CVD risk according to type of ADT exposure in experimental units

The CVD risk was similar for men treated in units with the highest proportion of GnRH agonist use and men treated in units with the lowest use (RR 1.01, 95% CI 0.93–1.11; Fig. 2 and Table 2).

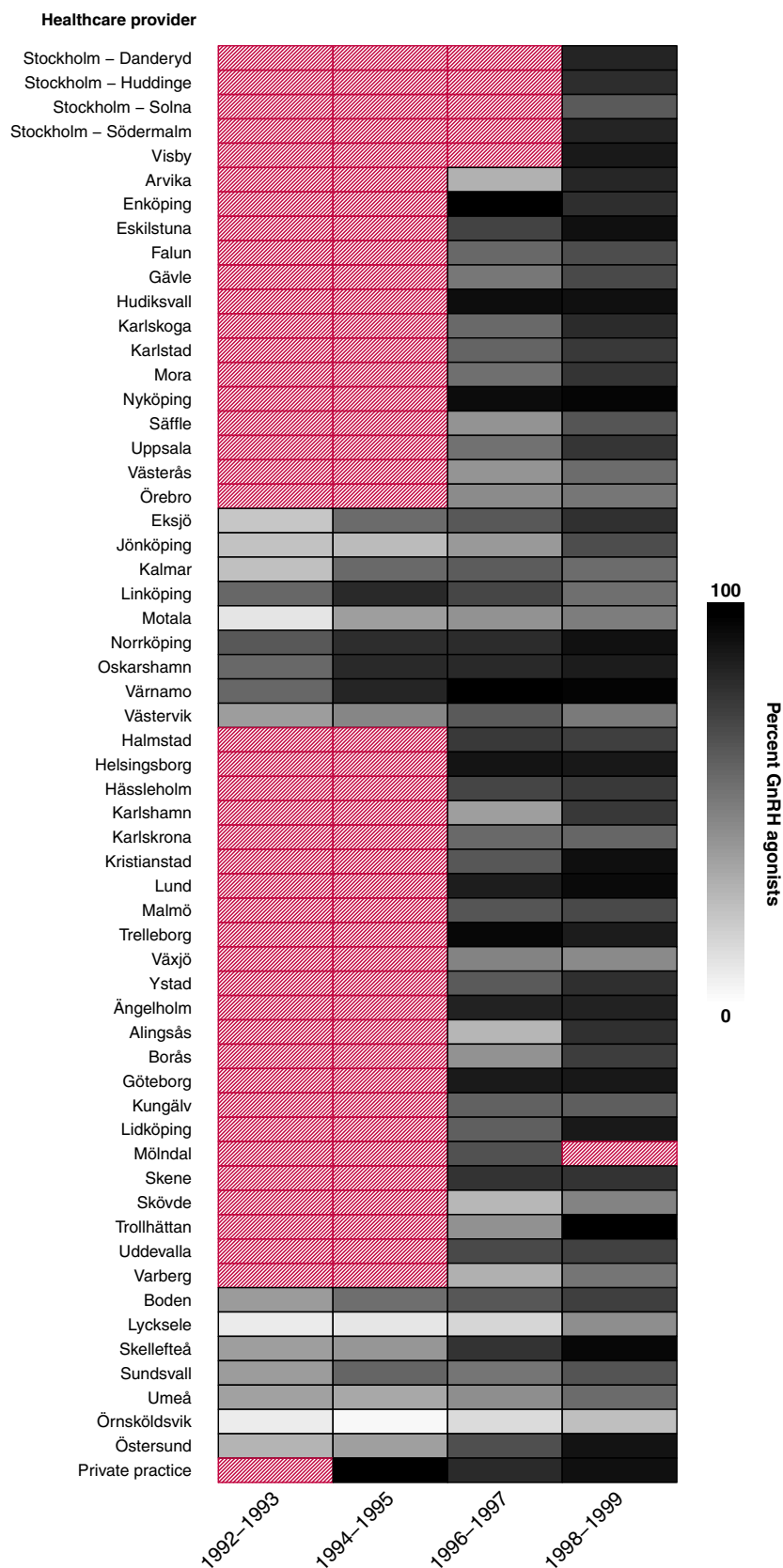


Fig. 1 – Percentage of men who received gonadotropin-releasing hormone (GnRH) agonists as primary treatment (ADT) by healthcare provider and time period in Prostate Cancer data Base Sweden (PCBaSe) 3.0. Men diagnosed by healthcare provider with <15 cases of primary androgen deprivation therapy per year during the specific time period were excluded (red rectangles). The National Prostate Cancer Register captured men diagnosed with prostate cancer in the Northern region from 1992, the Southeastern region from 1994, the Western, Southern, and Uppsala Örebro regions from 1996, and the Stockholm region from 1998.

Table 1 – Baseline characteristics for men with prostate cancer in Sweden 3.0 who received GnRH agonists or orchiectomy as primary treatment

	GnRH agonists as primary treatment in experimental unit		
	0–33%	34–66%	67–100%
Year of diagnosis			
1992–1993	31 (0–100)	12 (0–0)	2 (0–0)
1994–1995	19 (0–0)	11 (0–0)	6 (0–0)
1996–1997	41 (0–100)	34 (0–100)	31 (0–100)
1998–1999	9 (0–0)	43 (0–100)	61 (0–100)
Age at diagnosis			
Median	80 (75.5–83)	77 (72–82)	74 (66–77)
<70 yr	5 (0–0)	11 (0–0)	30 (0–100)
70–74 yr	11 (0–0)	23 (0–100)	22 (0–100)
75–79 yr	30 (0–100)	29 (0–100)	24 (0–0)
80+ yr	54 (0–100)	37 (0–100)	24 (0–0)
T stage			
T1a/b	3 (0–6)	2 (0–5)	2 (0–0)
T1c	2 (0–0)	4 (0–7)	6 (0–9)
T2	29 (14–48)	24 (15–36)	25 (12–39)
T3	51 (33–62)	52 (40–62)	52 (40–64)
T4	12 (0–19)	15 (5–21)	13 (0–20)
TX/missing	2 (0–0)	2 (0–3)	2 (0–0)
N stage			
N0	2 (0–0)	3 (0–4)	2 (0–3)
N1	2 (0–0)	3 (0–6)	6 (0–11)
NX/missing	96 (94–100)	94 (91–100)	91 (83–100)
M stage			
M0	20 (5–31)	25 (12–37)	31 (14–43)
M1	34 (22–48)	37 (25–52)	34 (21–50)
MX/missing	46 (22–67)	38 (13–56)	35 (12–50)
Prostate-specific antigen			
Median	87 (63.5–135.5)	79 (55–113)	65 (48.8–105.1)
<25 ng/ml	17 (7–22)	18 (10–23)	22 (11–29)
25–<50 ng/ml	16 (7–24)	19 (12–25)	19 (10–26)
50–<100 ng/ml	18 (10–25)	17 (11–25)	19 (11–26)
100–<200 ng/ml	15 (6–19)	14 (6–19)	13 (6–20)
200–<500 ng/ml	13 (4–20)	14 (6–19)	12 (6–18)
≥500 ng/ml	14 (5–22)	16 (9–21)	13 (6–20)
Missing	7 (0–10)	3 (0–5)	2 (0–0)
Gleason score ^a			
2–6	18 (6–24)	18 (8–25)	18 (9–27)
7	44 (30–55)	40 (27–54)	41 (28–50)
8–10	35 (24–48)	39 (25–50)	39 (26–50)
Missing	4 (0–6)	3 (0–5)	3 (0–4)
Charlson comorbidity index			
0	65 (57–75)	65 (59–77)	67 (58–79)
1	18 (10–24)	19 (11–24)	17 (9–22)
2+	17 (10–22)	16 (8–21)	16 (7–22)
Previous conditions within 5 yr before diagnosis			
Cardiovascular disease			
Yes	33 (22–41)	31 (19–40)	28 (17–37)
No	67 (59–78)	69 (60–81)	72 (63–83)
Hypertension			
Yes	6 (0–9)	7 (0–10)	6 (0–10)
No	94 (91–100)	93 (90–100)	94 (90–100)
Diabetes			
Yes	5 (0–10)	6 (0–10)	5 (0–7)
No	95 (90–100)	94 (90–100)	95 (93–100)
Education level			
Low	57 (50–75)	59 (52–70)	54 (44–68)
Middle	15 (5–22)	22 (12–31)	27 (15–36)
High	5 (0–10)	8 (0–14)	11 (0–17)
Missing	23 (0–33)	11 (0–13)	8 (0–6)
Marital status			
Unmarried	10 (0–15)	9 (0–12)	9 (1–15)
Married	63 (55–77)	65 (57–75)	69 (61–78)
Divorced	4 (0–6)	7 (0–12)	9 (0–14)
Widower	22 (7–29)	18 (4–25)	13 (0–17)
Missing	0 (0–0)	0 (0–0)	0 (0–0)

Table 1 (Continued)

	GnRH agonists as primary treatment in experimental unit		
	0–33%	34–66%	67–100%
Primary treatment			
GnRH agonists	19 (11–28)	53 (45–61)	87 (79–100)
Orchiectomy	81 (72–89)	47 (39–55)	13 (0–21)

GnRH = gonadotropin-releasing hormone.
Data are presented as total percentage/median with interquartile range between experimental units (ie, combination of year, hospital and age group) in parentheses.
^a World Health Organisation grade converted to Gleason score using the rule G1 = GS 2–6, G2 = GS 7, and G3 = GS 8–10.

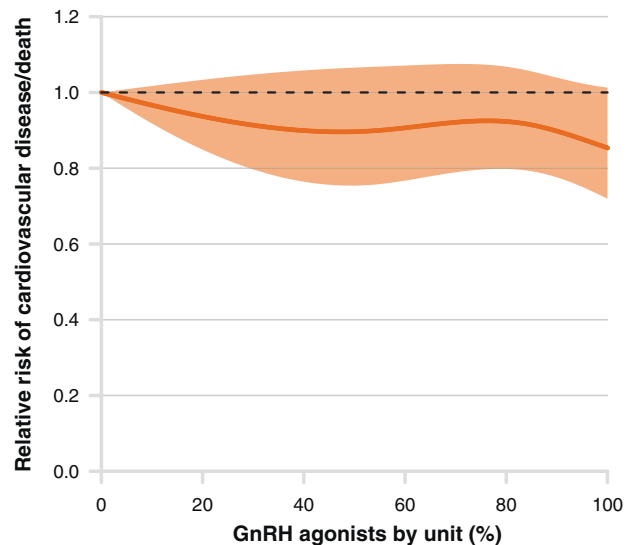


Fig. 2 – Relative risk of cardiovascular disease (CVD) according to the percentage of men who received gonadotropin-releasing hormone (GnRH) agonists as primary treatment in each experimental unit. The orange shading shows the 95% confidence interval. CVD was defined as first occurrence of CVD (ICD-10 codes I00–I99). The total number of CVD events was 5145, including 31% incident cases of other forms of heart disease (I30–I52), 26% ischaemic heart disease (I20–I25), 15% cerebrovascular disease (I60–I69), 11% hypertensive disease (I10–I15), 8% disease of the veins, lymphatic vessels, and lymph nodes (I80–I89), 5% disease of the arteries, arterioles, and capillaries (I70–I79), 3% pulmonary heart disease and disease of the pulmonary circulation (I26–I28), and 1% others and unspecified (I00–I09, I95–I99). Death from CVD was reported as the first occurrence of CVD in 8% of the men.

Table 2 – Relative risk of cardiovascular disease/death by percentage exposure to GnRH agonists

	RR (95% CI)	p value
GnRH agonists		
0–33%	1.00 (reference)	–
34–66%	1.04 (0.94–1.14)	0.5
67–100%	1.01 (0.93–1.11)	0.8

GnRH = gonadotropin-releasing hormone; RR = relative risk; CI = confidence interval.
Risk estimated using a Poisson model adjusted for T stage, M stage, Gleason score, prostate-specific antigen, previous cardiovascular disease, previous hypertension, and previous diabetes.

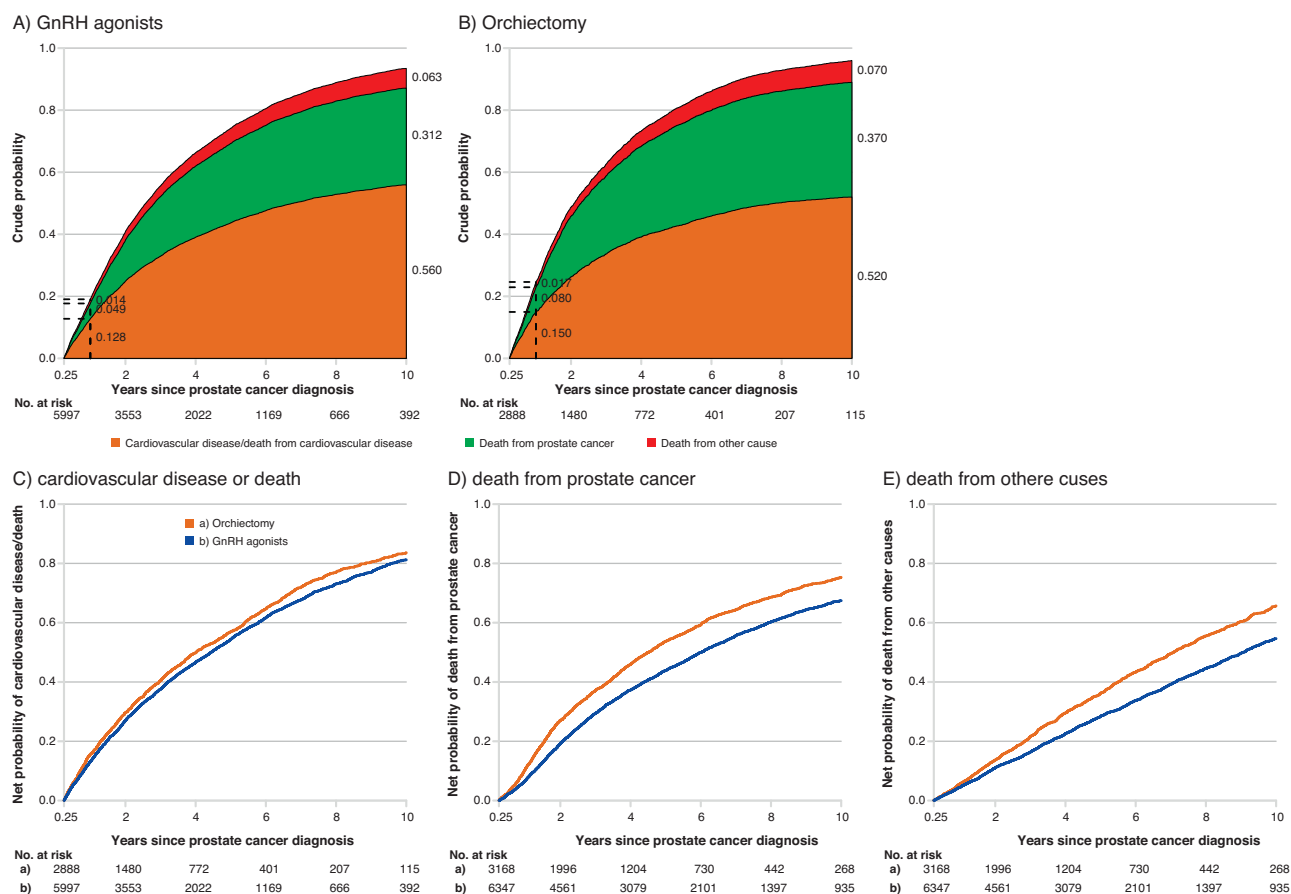


Fig. 3 – (A,B) Crude probability of death from cardiovascular disease (CVD), prostate cancer, or other causes for men who (A) received GnRH agonists and (B) underwent orchiectomy. (C–E) Net probability of (C) cardiovascular disease or death from cardiovascular disease, (D) death from prostate cancer, and (E) death from other causes for men who received GnRH agonists or orchiectomy. The crude probability is from competing-risks analysis of a CVD event and the competing events of death from prostate cancer and other causes. The net probability is from Kaplan-Meier analysis of CVD, prostate cancer death, and other causes of death.

3.2. Crude probability of CVD according to type of ADT

In total, 5145 CVD events were registered. The crude probability for CVD at 1 yr after diagnosis was lower for men on GnRH agonists (0.13 95% CI 0.12–0.14) than for men treated with orchiectomy (0.15, 95% CI 0.14–0.16) but was higher at 10-yr follow-up (0.56, 95% CI 0.55–0.57 vs 0.52, 95% CI 0.50–0.54; Fig. 3A,B). The 10-yr probability of death from prostate cancer was lower for men on GnRH agonists (0.31, 95% CI 0.30–0.32) than for men undergoing orchiectomy (0.37, 95% CI 0.35–0.39), but similar for death from other causes (0.06, 95% CI 0.06–0.07 vs 0.07, 95% CI 0.06–0.08).

3.3. Net probability of CVD according to type of ADT

In a multivariable Cox proportional hazards model, risk of CVD was similar for men treated with GnRH agonists and men treated with orchiectomy, (HR 1.02, 95% CI 0.96–1.09; Table 3). The CVD risk was higher among men with previous CVD (HR 2.03, 95% CI 1.90–2.17) and men with diabetes (HR 1.50, 95% CI 1.32–1.71). In an analysis restricted to CVD death as outcome, there was a higher risk after orchiectomy

compared to GnRH agonists on univariable analysis (Supplementary Fig. 2) but not multivariable analysis (Supplementary Table 2). There was a lower net probability of CVD during the first year after diagnosis for men on GnRH agonists compared to orchiectomy, and for prostate cancer death during the first 2 yr, whereas in subsequent follow-up the cumulative risks essentially increased in parallel (Fig. 3C,D). Finally, the risk of death from other causes was slightly higher after orchiectomy compared to GnRH agonists (Fig. 3E). Analyses stratified according to M stage and previous CVD yielded similar results as the main analyses (Supplementary Table 3). The risk of CVD as a continuous function of year of diagnosis was 1.02 (95% CI 1.00–1.04; $p = 0.017$).

4. Discussion

In this semi-ecologic, nationwide, population-based study, no evidence of higher risk of incident or fatal CVD was found for men on GnRH agonists compared to men who underwent orchiectomy. Supporting results were obtained in analyses of crude and net probabilities of CVD, with both exposure and outcome assessed on an individual level.

Table 3 – Multivariable Cox proportional hazards models^a of cardiovascular disease, fractures, and diabetes

	CVD ^a (n = 5145)		Fracture (n = 1262)		Diabetes ^b (n = 705)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Primary treatment						
Orchiectomy	1.00 (reference)		1.00 (reference)		1.00 (reference)	
GnRH agonists	1.02 (0.96–1.09)	0.5	0.91 (0.80–1.04)	0.16	1.02 (0.85–1.22)	0.8
Year of diagnosis (continuous)	1.02 (1.00–1.04)	0.017	1.11 (1.07–1.15)	<0.001	1.02 (0.98–1.07)	0.3
T stage						
T1	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
T2	0.97 (0.86–1.09)	0.6	0.88 (0.70–1.09)	0.2	1.20 (0.86–1.67)	0.3
T3	0.97 (0.87–1.09)	0.6	0.89 (0.72–1.11)	0.3	1.22 (0.89–1.68)	0.2
T4	1.02 (0.89–1.17)	0.8	1.07 (0.82–1.40)	0.6	1.19 (0.80–1.76)	0.4
M stage						
M0/MX	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
M1	1.00 (0.93–1.08)	0.9	1.32 (1.14–1.53)	<0.001	1.06 (0.87–1.29)	0.6
Prostate-specific antigen						
<25 ng/ml	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
25–<50 ng/ml	0.97 (0.89–1.05)	0.5	1.04 (0.88–1.23)	0.7	0.83 (0.67–1.04)	0.11
50–<100 ng/ml	1.03 (0.95–1.12)	0.5	1.00 (0.84–1.19)	1	0.86 (0.68–1.08)	0.19
100–<200 ng/ml	1.07 (0.97–1.18)	0.19	1.22 (1.01–1.49)	0.043	0.83 (0.63–1.09)	0.18
200–<500 ng/ml	1.09 (0.98–1.22)	0.11	1.11 (0.89–1.38)	0.4	1.25 (0.96–1.63)	0.10
≥500 ng/ml	1.05 (0.93–1.18)	0.4	1.01 (0.79–1.29)	0.9	0.93 (0.68–1.28)	0.7
Gleason score						
2–6	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
7	1.01 (0.93–1.08)	0.9	1.09 (0.94–1.27)	0.2	1.18 (0.96–1.44)	0.12
8–10	1.10 (1.01–1.18)	0.022	1.09 (0.93–1.27)	0.3	1.20 (0.97–1.49)	0.09
Previous CVD ^c						
No	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Yes	2.03 (1.90–2.17)	<0.001	1.04 (0.90–1.21)	0.6	1.11 (0.91–1.35)	0.3
Previous hypertension ^c						
No	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Yes	1.13 (1.00–1.28)	0.051	1.14 (0.88–1.49)	0.3	1.33 (0.93–1.91)	0.12
Previous diabetes ^c						
No	1.00 (reference)	–	1.00 (reference)	–		
Yes	1.50 (1.32–1.71)	<0.001	1.43 (1.08–1.88)	0.012		

CVD = cardiovascular disease; GnRH = gonadotropin-releasing hormone.

^a All models performed with age as time-scale.^a A total of 564 (11%) men had hypertension as their first CVD event.^b Only men without previous diabetes before their prostate cancer diagnosis.^c Within 5 yr before prostate cancer diagnosis.

The main limitation of the present study regarding exposure was the nonrandom allocation to type of ADT, with ensuing selection bias for younger and healthier men with less advanced cancer to receive GnRH agonists. Thus, despite the semi-ecologic design, residual confounding cannot be excluded. Since the NPCR does not register date of treatment, we started follow-up 3 mo after the date of diagnosis, at which time point 90% of men diagnosed in a later calendar period had received their primary treatment. There was no information on duration and adherence to GnRH agonists, but it is rare for men with advanced prostate cancer to stop ADT. We also lacked information on smoking, body mass index, and use of cardiovascular drugs. Limitations regarding the endpoints are that we used administrative data from the Patient Registry and the Cause of Death Registry to define CVD events. However, several investigations have shown high validity for diagnosis of CVD (eg, heart failure, acute myocardial infarction, and stroke) [34–37] and there are no reasons to assume a systematic bias according to type of ADT. Strengths of the study included the nationwide, population-based cohort of men with comprehensive data from several high-quality health care registers [23–26] as well as the use of three different

statistical methods to assess the association between type of ADT and risk of CVD.

In accordance with previous studies, men treated with orchiectomy for prostate cancer in the current study were older, had more comorbidities, and presented with more advanced stage of prostate cancer compared to men treated with GnRH agonists [12,17–19]. A meta-analysis including 12 randomised clinical trials found no difference in overall or prostate cancer survival between men treated with GnRH agonists and orchiectomy [38]. Accordingly, the higher rate of prostate cancer death among men treated with orchiectomy in our study was the result of more advanced cancer in comparison to men on GnRH agonists, which in turn influenced the risk of CVD. The semi-ecologic study design decreased the influence of an individual's cancer characteristics and general health on selection of ADT, but did not fully eliminate it. However, the risk of CVD among men treated in units with high use of GnRH agonists was similar to that in units with low use.

In separate analyses, we determined the net and crude probability of death from CVD, prostate cancer, and other causes. Crude probability is estimated using a competing-risks analysis in which death from causes other than the

event of interest is treated as a competing event. Thus, the crude probability of CVD will be decreased by a high number of competing events (eg, death from prostate cancer). At 10-yr follow-up, men on GnRH agonists in our study had a higher probability of CVD and a lower probability of prostate cancer death in comparison to men who underwent orchiectomy.

Net probability refers to the hypothetical situation in which only the event of interest can occur. All other events are censored and there is no influence from competing events on risk; this is the preferred study design for investigating causality [39]. We found that the net probability of both CVD and prostate cancer death were higher for men who underwent orchiectomy than for men on GnRH agonists. The results from these head-to-head comparisons are in accordance with a Chinese study of 297 men on GnRH agonists and 387 men who underwent orchiectomy [19]. Furthermore, previous studies using PCBaSe that included 5000 men who underwent orchiectomy and 20 000 men on GnRH agonists showed that these two ADT modalities were associated with a similar increase in CVD risk and fracture risk in comparison to the background male population [5,12,13,40].

By contrast, our results differ from those of three other large observational studies [14,17,18]. Two of the studies, a Surveillance, Epidemiology and End Results (SEER)–Medicare database study including 73 196 men with locoregional prostate cancer [14] and a Danish nationwide, population-based study including more than 30 000 prostate cancer cases [18], investigated the risk of CVD for men managed with orchiectomy or medical ADT (in the Danish study both GnRH agonists and antiandrogens) to that for men with prostate cancer not on ADT. Both studies found a higher risk of CVD for men on GnRH agonists compared to men not on ADT, whereas the risk of CVD was similar for men who had undergone orchiectomy and men not on ADT.

The third study, also a SEER study, included men with metastatic prostate cancer primarily managed with ADT during a 15-yr period, of whom 2866 men received GnRH agonists and 429 men underwent orchiectomy. In a direct comparison between the two ADT modalities, the crude probability of CVD and of fractures and diabetes was lower after orchiectomy in comparison to GnRH agonists [17]. It is difficult to conceive a biological mechanism for the lower risk of fractures after orchiectomy compared to GnRH agonists. The risk of fractures increases with lower levels of androgens [41,42] and, on average, androgen levels are slightly higher in men on GnRH agonists than in men who have undergone orchiectomy [43]. Thus, confounding is a likely explanation for the unexpected results for fractures and could also have contributed to the association with CVD. Furthermore, in this SEER study, there was no statistically significant difference in net probability, the preferred method for investigation of causality, between GnRH agonists and orchiectomy for any outcome, in accordance with our results.

Taken together, the results from our study and all the cited studies do not provide evidence that warrants a change in the recommendations for use of ADT for advanced prostate cancer from GnRH agonists to orchiectomy.

5. Conclusions

In this nationwide, population-based observational study there was no increase in the risk of CVD among men on GnRH agonists compared to men who had undergone orchiectomy in three separate analytical approaches. Our study provides no evidence in favour of changing the current standard ADT for prostate cancer.

Author contributions: Fredrik Sandin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stattin, Thomsen, Garmo, Sandin.

Acquisition of data: Stattin, Robinson, Lissbrant, Ahlgren.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Thomsen, Stattin.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Sandin, Garmo, Stattin, Thomsen.

Obtaining funding: Stattin.

Administrative, technical, or material support: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2017.06.036>.

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